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EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	**PAPER NUMBER**
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/03/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/088,567	AKIRA ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *1/11/2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-19,32-37 and 2130* is/are pending in the application.

4a) Of the above claim(s) *8-16,21-30 and 32-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-19 and 35-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment filed on January 11, 2007 has been received and entered. Applicants have canceled claims 1-7, 20 and 31, while claims 17-19 have been amended. Applicant has also added claims 35-37.

Election/Restrictions

Applicants' election of claims 17-20 and 31 (Group IV) in the reply filed on July 18, 2006 was acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 8-16, 21-30 and 32-34 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on July 18, 2006.

Claims 17-19 and 35-37 are under current examination.

Priority

Applicant's submission of certified English translation of foreign priority document for application, JP 2000-219652 is acknowledged.

New- Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 17-19 and 35-37 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well-established utility.

Claims 17 is directed to a transgenic mouse comprising in its genome a gene encoding any receptor protein that is excessively expressed specifically recognizing bacterial DNA having an unmethylated CpG sequence. Claim 18 is directed to a knockout mouse lacking a functional gene encoding a receptor protein specifically recognizing bacterial DNA having an unmethylated CpG sequence. Claim 19 limits the mouse to include macrophage derived from said mouse shows no reactivity against bacterial DNA having unmethylated CpG sequence. Claim 35 is directed to a transgenic mouse comprising in its genome a homozygous inactivation of Toll like receptor (TLR9) allele such that non functional N-terminal fragment of TLR-9 is produced, wherein macrophage of said mouse exhibit decreased responsiveness to CpG ODN. Claims are also directed to a knockout mouse lacking receptor protein lacking proteins specifically recognizing bacterial DNA having an unmethylated CpG sequence. In the instant case, claimed transgenic mice are not supported by a specific and substantial asserted utility or a well-established utility because the specification fails to assert any specific and substantial asserted utility for the claimed transgenic mice.

The specification teaches that any DNA derived from bacteria such as an oligodeoxynucleotide having an unmethylated CpG motif activates immune cells such as T-cells, B-cells and antigen-presenting cells, and induces immune response can be used such as DNA derived from plurality of bacteria. The disclosure states that the knockout mice lacking TLR9 of the present invention could be used to elucidate functional mechanisms of bacterial DNA and others having an unmethylated CpG sequence and to developing vaccine against bacterial infections (see page 14 of the specification). In addition, specification contemplates the transgenic mice of the invention would be useful to diagnose and treat bacterial diseases and also elucidate functional mechanisms of DNA derived from bacteria at the molecular level (see page 25, para. 2). The invention embraces a transgenic mouse comprising in its genome a gene encoding any receptor protein specifically recognizing bacterial DNA that having

an unmethylated CpG sequence that is expressed. The specification also embraces a knockout whose genome comprises a homozygous inactivation of TLR9 gene resulting in prevention of expression of a functional TLR9 protein in cells of the mouse. In some embodiments, the mouse lacks the functional gene encoding the receptor protein recognizing bacterial DNA having CpG sequence more specifically a mouse comprising a homozygous disruption of the TLR9 such that no functional N-terminal fragment of TLR is produced and wherein macrophage derived from such mouse exhibit decreased responsiveness to CpG ODN. Furthermore, specification contemplates instant knockout mice lacking TLR9 could be used to elucidate functional mechanisms of bacterial DNA and others having an unmethylated CpG sequence and to developing vaccine against bacterial infections (page no 14). It is noted that art of record indicate that that DNA vaccine elicits immune responses by multiple mechanisms and role of TLR9 is not essential for the induction of immune responses following DNA immunization (see Babiuk et al Immunology 2004 113 114–120; Figure 2, page 117, col. 1, para. 1). It is apparent that instant specification has not provided adequate guidance as to how an artisan would have used the TLR knockout or TLR over expressing mouse in developing vaccine against bacterial infection. In absence of any specific teaching an artisan of skill would have to perform undue experimentation to make use of the invention. It is noted that neither specification nor art of record discloses that instant transgenic and or knockout mouse phenotype is associated with any disease condition or model for any disorder. The specification does not provide any immune response in transgenic mouse of the invention. The specification fails to disclose any asserted utility for the mouse as a model or for a method of identifying therapeutic agent or disease model that could explicitly indicates the role of TLR9 in any of the physiological disorder that are found to be specific and/or substantial.

At the time of filing of instant application, an artisan would have not found such utilities evident because specification does not provide a correlation between a TLR9 over expression or lack of expression and established function, phenotype or disease. There is no specific teaching as to the role of TLR9 in a particular disease or disorder. The specification discloses no nexus between TLR9 and any known pathological state

nor does provide adequate guidance how it could be used in developing vaccine against bacterial infection. The specification does not provide any phenotype by any mouse that overexpresses any gene encoding a receptor protein specifically recognizing bacterial DNA having unmethylated CpG sequence. In fact, no such transgenic mouse over expressing TLR9 is disclosed. Furthermore, specification has only exemplified a TLR9 knockout mouse showing less response against bacterial DNA. It is noted that specification shows a comparison of immunological characteristics by measuring TNF alpha, IL-6 or IL-12 production induced by CpG ODN, PGN or LPS in TLR9 knockout and wild type mice (see figure 5-9). However, specification fails to correlate various immunological parameters to any specific disease or condition. It is emphasized that macrophage obtained from transgenic TLR9 knockout mouse of invention showing decreased responsiveness to CpG ODN is not a specific, substantial asserted utility or a well-established utility. Prior to instant invention, Holschneider et al. (Int J Devl Neuroscience, 2000, 18: 615-618, art of record) who describes that single genes are often essential in a number of different physiological processes. Hence, deletion of an individual gene may prove so drastic or so widespread as to create an amalgam of phenotypes whose interpretation becomes confounded by the interaction of various new physiologic changes (pp 615). Holschneider et al discuss various factors that contribute to the resulting phenotype of transgenic mice, including compensatory system that may be activated to mask the resulting phenotype; these compensatory changes may be due to differential expression of another gene, which may be regulated by the downstream product of the deleted gene. This is further evident in several post filing art showing that role of TLR9 is not essential for the induction of immune responses following DNA immunization and recognition of CpG-ODN being more complex than previously reported (supra). The specification of the instant application fails to provide any correlation between the disclosed phenotypes and function or role of TLR9 knockout or transgenic over expressing TLR9 in any specific disease or any disorder. Thus, in order to determine the specific utility for any such knockout or transgenic mouse over expressing TLR9 mice. In the instant case, Artisan of skill would have to perform further research upon the claimed mouse in order to establish a nexus between the knockouts

or transgenic mouse and the observed phenotypes relating to different mechanism and other specific utility as described in the specification (see page 14, para. 1 of the specification). It is emphasized that applicants do not provide any nexus between over expression of TLR9 or deletions of gene to any specific condition or disease that could be directly attributed to the over expression or deletion of the TLR9 gene. Thus, asserted utility of using the mice to study the mechanism and development of vaccine against bacterial infection is not substantial or creditable because specification does not identify any does not disclose a mouse that shows phenotype consistent with any disorders or condition, rather it provides invitation to other to further research the mouse for specific and substantial utility.

As set forth in the utility guideline a general statement of any specific utility, such as knockout mice lacking TLR9 to elucidate functional mechanisms of bacterial DNA and others having an unmethylated CpG sequence and to developing vaccine against bacterial infections (see page 14, para. 1, lines 5-7 and page 25, para. 2) would ordinarily be insufficient. Similarly, a statement of utility for plurality of screening method in transgenic or knockout mouse of the invention is non-specific, renders the purported utility of the claimed mice to be non-specific. The usefulness of the transgenic or knockout mouse, as models for functional mechanisms of bacterial DNA and others having an unmethylated CpG sequence and to developing vaccine against bacterial infections or related disease, is not clear, absence of assessment that they reflect a particular diseases state. This leaves the Artisan of skill to speculate the uses of the mice. Under the utility guideline set forth above requirement for further research or experimentation renders the claimed invention as lacking in a specific or substantial utility. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real-world" context of use are considered substantial utilities. The evidence of record has not provided any other utility for the transgenic and knockout mice encompassed by the claims that are substantial and specific. Since the mice have no determined specific function, the relation to any disease or condition is unknown. Furthermore, because the phenotypes in the transgenic mice over expressing TLR9 and a TLR9 knockout mice are not specific to any condition, the Artisan, at the time of filing,

would not know how to use the mouse or any data resulting from using the mice. To make such a determination, the Artisan of skill would need to further research to mice, to determine if functions associated with over expression or lack of expression of TLR9 are present in the mice, and then identify disease or condition associated with the disclosed phenotype. The specific utilities cited in the disclosure require further research to establish whether deletion or over expression of TLR9 can be attributed to a particular function or utility. The invention of claims 17-19 and 35-37 provide no specific and substantial utility, since no function can be attributed to the mouse showing over expression or lack of expression of TLR9, would also have no specific and substantial utility.

Claims 17-19 and 35-37 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

New Grounds of Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-19 and 35-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

The office has analyzed the specification in direct accordance to the factors outlines in *In re Wands*. MPEP 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on factors discussed in MPEP 2164.01(a) and the evidence as whole, it is not necessary to discuss each factor in written enablement rejection." These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

Claims 17-19 and newly added claim 35-37are broad in scope. The following paragraph will outline the full scope of the claims. These claims are broad in scope, encompassing transgenic mouse comprising any gene encoding a receptor protein specifically recognizing bacterial DNA having an unmethylated CpG sequence that is either expressed or inactivated. The disclosure provided by the applicant, in view of prior art, must encompass a wide area of knowledge to a reasonably comprehensive extent. In other word each of those, aspect considered broad must be shown to a reasonable extent so that one of the ordinary skills in the art at the time of invention by applicant would be able to practice the invention without any undue burden being on such Artisan.

The invention features methods of making transgenic mouse excessively expressing a gene encoding a receptor protein specifically recognizing bacterial DNA having the unmethylated CpG sequence such that said mouse producing a large

amount of receptor proteins specifically recognizing bacterial DNA having an unmethylated CpG sequence compared with wild-type non-human animals (see page 11, last paragraph of the specification). It is also noted that claim 18 embraces knockout mouse lacking a functional gene encoding a receptor protein specifically recognizing bacterial DNA having an unmethylated CpG sequence. The specification while provides guidance for a method to make transgenic TLR 9 knockout mouse using ES cell. However, it does not provide any guidance how to use the exemplified mouse in any specific disease or condition or make other knockout mouse comprising any other gene encoding a receptor protein specifically recognizing bacterial DNA that could be used or correlated to any specific condition as contemplated in the instant application.

Claims are directed to the creation of transgenic mouse lacking functional gene encoding any receptor protein specifically recognizing bacterial DNA. Claims are directed to a transgenic mouse whose genome comprises inactivation of TLR9 allele such that no functional N-terminal fragments of TLR-9 is produced, wherein macrophage of said mouse exhibit decreased responsiveness to CpG ODN. The specification has contemplated introducing a targeting constructs in mouse embryonic stem cell by homologous recombination, and microinjecting said mouse embryonic stem cell into mouse blastocysts; and implanting the blastocysts comprising the mouse embryonic stem cell into pseudo pregnant mouse and then allowing the resulting pregnant mouse to deliver viable chimeric offspring and then producing a transgenic TLR9 knock out mouse. The specification has exemplified TLR9 knockout mouse whose macrophage show no reactivity against bacterial DNA having an unmethylated CpG sequence (see example 2-4, page 20-22). It is noted that the specification does not provides adequate correlation between phenotype obtained to any specific physiological condition or disease. In addition, specification also does not provide any evidence to suggest that phenotype seen in TLR9 knockout mouse would be same in any other transgenic knockout lacking functional gene encoding any other receptor protein that recognizes CpG sequence. The data as presented does not disclose a coherent picture of the function of any gene encoding a receptor protein that recognizes CpG sequence or any specific condition associated with TLR9 knockout. In absence of

any specific phenotype linking the mouse to any specific condition or disease, an artisan would not know whether macrophage having reduced reactivity to unmethylated CpG sequence is due to TLR9 knockout or it is because of other compensatory factors. The skilled artisan would have to further research and such research would constitute undue experimentation to make use of the invention. In addition, claims are also directed to creation of transgenic mouse lacking functional gene encoding any receptor protein specifically recognizing bacterial DNA. Prior to instant invention, the art teaches the feasibility of creating a homozygous disruption of a targeted gene of interest and the creation of transgenic mouse containing the same. However, the art also teaches the resulting phenotype of a knockout mouse is exceedingly unpredictable. For example, Leonard (Immunological Reviews, 1995, 148: 98-114, art of record) discloses mice with disruption in the gc gene that was intended to be a model for X-linked severe combined immunodeficiency (XCIDS), but displays a variety of unexpected traits (Abstract). These knockout mice were expected to have thymocytes with decreased proliferation in response to stimulation with antibodies, but the thymocytes proliferated normally (pp 105, line 7). Griffiths (Microscopy Research and Technique 1998, 41: 344-358) taught that, despite a known role for the PLP gene based on spontaneous mutations in the gene, the knockout mouse failed to display any of the expected phenotype (pp 350, last paragraph). Furthermore, the state of the art suggests such unpredictability of phenotype is correlative to the genetic background of the knockout mouse. For example, Keri et al., (Proc Natl Acad Sci U S A. 2000; 97(1): 383-7) show that elevated levels of lutenizing hormone in transgenic can result in different reproductive system abnormalities including ovarian tumors. Schoonjans et al (Stem Cells, 2003; 21:90-97), for example state that the phenotype of gene-targeted mice is not only due to genetic alteration itself but also to the genetic background in which it is generated (pp93, discussion). Wolfer et al (Trends in Neuroscience, 2002, 25 (7): 336-340) describe the unpredictability of phenotype resulting from gene disruption can influenced by gene flanking the disrupted coding sequence and by the general genetic background of mouse strains, wherein congenic strains carrying the same null mutation can sometime show widely divergent phenotypes (pp 336, column 1-3). Thus, at the time of filing, it is

evident from the art of record that the resulting phenotype of a homozygous knockout mouse was considered unpredictable and the specification does not provide any evidence to suggest that macrophage isolated from transgenic knockout mouse lacking functional gene encoding any receptor protein specifically recognizing bacterial DNA would show phenotype that would specific to deletion of gene encoding any receptor protein recognizing CpG sequence. The guidance provided by the specification amounts to invitation for the skilled Artisan to try and follow the disclosed instructions to make use of the claimed invention. Claims 18-19 embrace transgenic knockout mouse that lacks gene encoding a receptor protein recognizing CpG sequence. The specification describes a targeting vector that is constructed by replacing a 1.0 kb fragment encoding part of LRR (leucine-rich repeat) region with a neomycin-resistance gene cassette (see example 2). At the time of filing of this application, Holschneider et al. (Int J Devl Neuroscience, 2000, 18: 615-618) state that single genes are often essential in a number of different physiological processes. Hence, deletion of an individual gene may prove so drastic or so widespread as to create an amalgam of phenotypes whose interpretation becomes confounded by the interaction of various new physiologic changes (pp 615). Holschneider et al discuss various factors that contribute to the resulting phenotype of transgenic mice, including compensatory system that may be activated to mask the resulting phenotype; these compensatory changes may be due to differential expression of another gene, which may be regulated by the downstream product of the deleted gene. Thus, at the time of filing, the resulting phenotype of a knockout mouse was considered unpredictable and it was confounded by multiple compensatory pathways. The specification does not disclose a transgenic mouse comprising it its genome inactivation of any gene encoding a receptor protein other then TLR9 and specifically recognizing bacterial DNA having the unmethylated CpG sequence. It is emphasized that the resulting phenotype of exemplified TLR9 knockout does not show any nexus between the deletion of gene to any specific physiological condition or disease. An artisan would have to perform undue experimentation to make use of exemplified TLR9 knockout mouse showing decreased responsiveness to CpG ODN. The specification contemplate instant knockout mice lacking TLR9 could be used

to elucidate functional mechanisms of bacterial DNA and others having an unmethylated CpG sequence and to developing vaccine against bacterial infections (page 14 and page 25). The specification does not provide any guidance to establish any nexus between TLR9 knockout to the immune response generated against any bacterial infection. It is apparent that instant specification has not provided adequate guidance as to how an artisan would have used the TLR knockout mouse exemplified in this application. In absence of any specific teaching an artisan of skill would have to perform undue experimentation to make and use of the invention.

Claims 17and 37 is directed to a nonhuman animal wherein gene encoding a receptor protein is excessively expressed subsequently limiting gene to include TLR9. The specification describes a non-human animal excessively expressing a gene encoding a receptor protein specifically recognizing bacterial DNA having the unmethylated CpG sequence of the present invention can be any transgenic mouse producing a large amount of receptor proteins specifically recognizing bacterial DNA having an unmethylated CpG sequence compared with wild-type non-human animals (see page 11, last paragraph). It is noted that as recited claim 17 read on transgenic mouse over expressing gene-encoding protein that recognizes bacterial DNA or any mouse whose host cell express such gene. The specification does not provide any specific guidance as to how gene-encoding protein that recognizes bacterial DNA will be expressed at high level showing any specific phenotype correlating to any conidtion. Although great advances have occurred in transgenic technology, the state of the art of generating transgenic animals is such that the resulting phenotype would not be predictable. This is because the art of transgenic animals has for many years stated that the unpredictability lies with the site or sites of integration of the transgene into the target genome. Transgenic animals are regarded to have within their cells cellular mechanisms which prevent expression of the transgene, such that DNA methylation or deletion from the genome (Kappell et al Current Opinions in Biotechnology 3, p. 549, col 2, par 2, 1992). The elements of the particular construct used to make transgenic animals are held to be critical, and that they must be designed case by case without general rules to obtain good expression (e.g. specific promoters, presence or absence

of introns, etc. (Houdebine J. Biotech 34:281, 1994). Cameron (Cameron ER, Molecular Biotechnology 7: 253-265, 1997) noted, " Well regulated transgene expression is the key to successful transgenic work, but all too often experiments are blighted by poor levels or complete absence of expression, as well as less common problems, such as leaky expression in non targeted tissues. A feature common to any transgenic experiments is unpredictable transgenic lines produced with same construct frequently displaying different levels of expression. Further, expression levels do not correlate with number of transgene copies integrated. Such copy number independent expression pattern emphasizes the influence of surrounding chromatin on the transgene" (pp 256; section 4 on transgene regulation and expression). Furthermore, Sigmund states that the random nature of transgene insertion, resulting founder mice can contain the transgene at a different chromosomal site, and that the position of the transgene effects expression, and thus the observed phenotype (Sigmund et al Arteroscler Throm Vasc Biol 20:1426, col 1, par 1, lines 1-7, 2000). With regard to the importance of promoter selection, Niemann states that transgenic pigs made with different promoters regulating expression of growth hormone gene give disparate phenotypes, one deleterious to the pig, the compatible with pig health (Neimann Trans Res 7:73, col 2, par 2, line 12 to p. 73, col 1, line 4, 1998). While the intent is not to say transgenic animals of a particular phenotype can never be made, the intent is to provide art taught reasoning as to why the instant claims are not enabled. Given differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification for any transgenic mouse, it would have required undue experimentation to the levels of the transgene product, the consequences of that product, and therefore, the resulting phenotype. The specification fails to provide teachings or specific guidance to overcome the above-described unpredictabilities. It is emphasized that to successfully produce a transgenic mouse with a specific phenotype, an artisan would have to perform undue experimentation to select appropriate promoter and other elements in construct to obtain appropriate level of expression resulting in a specific phenotype and correlating any such phenotype to specific function in a disease process or physiological condition.

In view of the lack of teachings or guidance provided by the specification with regard to an enabled transgenic mouse comprising a gene encoding that recognizes a bacterial DNA that is either expressed or deleted, the lack of teaching or guidance provided by the specifications to overcome the art recognized unpredictability of expression pattern, resulting phenotype and for the specific reasons cited above it would have required undue experimentation for an artisan of skill to make and use the claimed invention. It would require undue experimentation for an Artisan to make and use the claimed invention and/or working examples demonstrating the same, such invention as claimed by the applicant is not enabled for the claimed inventions.

Maintained-Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-19 and newly added claim 36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claim embraces a gene encoding a receptor protein specifically recognizing bacterial DNA having unmethylated CpG sequence.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." *Vas-cath Inc. v. Mahurkar*, 19USPQ2d at 1 117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *Vas-cath Inc. v. Mahurkar*, 19USPQ2d at 1116.

As recited claims embrace any gene sequences encoding receptor protein specifically recognizing bacterial DNA having an unmethylated CpG sequence from all species. Based upon the prior art there is expected to be sequence variation among the species of DNA sequences of gene from different species. The specification has provided the description of mice TLR-9 sequence showing contemplated biological activity. The specification however has not disclosed the sequences of any of the other gene embraced by the claims. There is no evidence on the record of a relationship between the structures of the DNA molecules of any of the embraced gene encoding a receptor protein such as TLR9 that would provide any reliable information about the structure of DNA molecules within the genus. There is no evidence on the record that embraced gene encoding a receptor protein specifically recognizing bacterial DNA had known structural relationships to each other; the art indicated that there is variation between DNA sequences of various gene sequences. The claimed invention as a whole is not adequately described if the claims require essential or critical elements or motifs which are not adequately described in the specification and which is not conventional in the art as of applicants effective filing date. Additionally, to the extent that the claims are intended to encompass DNA encoding receptor protein specifically recognizing bacterial DNA by hybridizing mouse derived DNA library with part or whole of a sequence of bases shown in SEQ ID NO: 1 or its complimentary sequence under stringent condition (see specification page 7 last paragraph and page 8, first paragraph). Thus, it is apparent that hybridization is also contemplated in the specification, however the specification does not provide any functional properties to the resulting sequence. There is no evidence on the record of a relationship between the structures of the DNA molecules of any of the sequence that would provide any reliable information about the structure of DNA molecules within the genus. In addition, specification fails to provide any guidance to how modification to one species disclosed can be made while maintaining the required biological activity. For example, a sequence of 20 to100 base pairs from the SEQ ID NO 1 as disclosed in the specification will hybridize, however if it does not contain the essential motifs that are required for contemplated biological activity, such a sequence will hybridize to SEQ ID NO: 1 but will not be functional and

show contemplated biological activity. The specification does not provide any disclosure as to what would have been the required structure for a complimentary sequence or small fragments, or sequence that will hybridize and whether the structure is present in various species of mammals or how does it vary. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *Pfaff v. Wells Electronics. Inc.*, 48 USPQ2d 1641, 1646 (1998). In the instant case, the claimed embodiments of gene encoding a receptor protein specifically recognizing bacterial DNA sequence, other than the mice TLR9 sequence encompassed within the genus of such gene sequences lack a written description. The specification fails to describe what DNA molecules fall into this genus. The skilled artisan cannot envision the detailed chemical structure of the encompassed gene sequences showing contemplated biological activity, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).
One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 UsPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF'S were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In view of the above considerations, one of skill in the art would not recognize that applicant was in possession of the necessary common features or attributes possessed by member of the genus of gene sequences encoding a receptor protein that specifically recognizes bacterial DNA, other than the mouse TLR9 sequence. Moreover, the art has recognized that there would be variation among the species of the genus of DNA sequences of such gene sequences.

Therefore, Applicant was not in possession of the genus of gene sequences encoding a receptor protein that specifically recognizes bacterial DNA as encompassed by the claims. *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1404, 1405 held that to fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention."

Response to Arguments

Applicant's arguments filed January 11, 2007 have been fully considered but they are not fully persuasive. Applicants in their argument on page 8, summarize that applicants' disclosure of for gene for example TLR9 is adequate for the breadth of the claims. In response, it is emphasized that the claimed embodiments of a transgenic mouse that either lacks or overexpresses any receptor sequence specifically recognizing bacterial DNA having an unmethylated CpgG sequence other than the TLR9 within the genus of sequence that may recognize bacterial DNA having CpG sequence lack a written description because specification fails to describe what other gene sequence fall into this genus. In addition, the specification does not provide any structure or motifs that may be required for the contemplated biological activity. Furthermore, it is noted that specification teaches that sequence may encompass DNA encoding receptor protein specifically recognizing bacterial DNA by hybridizing mouse derived DNA library with part or whole of a sequence of bases shown in SEQ ID NO: 1 or its complimentary sequence under stringent condition (see specification page 7 last paragraph and page 8, first paragraph). In absence of any specific guidance an skilled artisan cannot envision the detailed chemical structure of the encompassed by sequences that would specifically recognize unmethylated CpG sequence, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation.

Withdrawn-Claim Rejections - 35 USC § 112

Claims 17-19 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of amendment to the claim and cancellation of claim 20 and 31.

Withdrawn-Claim Rejections - 35 USC § 102

Claims 17-20 and 31 rejected under 35 U.S.C. 102(e) as being anticipated by Bauer et al (US Patent No 6,943,240, dated 9/13/2005; effective filing date 9/15/2000) is withdrawn in view of applicant's submission of certified English translation of the foreign priority document. It is noted that claimed subject matter were in fact disclosed in the foreign priority document.

Claims 18-19 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Takeuchi et al (Immunity, Oct. 1999, 11, 443-452) is withdrawn. Examiner would agree that TLR-2 would specifically recognize bacterial cell wall and not CpG sequence as required by the claim.

Claims 18-19 and 31 are rejected under 35 U.S.C. 102(a) as being anticipated by Hemmi et al (Nature. 2000 Dec 7; 408(6813): 740-5) is withdrawn in view of applicant's submission of certified English translation of the foreign priority document. It is noted that claimed subject matter were in fact disclosed in the foreign priority document.

Withdrawn-Double Patenting

Claims 18-19 and 31 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of copending Application No. 10/517,663 (US Patent Publication no 2006/0059579) is withdrawn in

view of amendments to the claims in '579. It is noted that amendment in '663 distinguishes claims pending in this application.

Conclusion

No Claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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